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Original Article

Radical hysterectomy or chemoradiotherapy for clinically early-stage cervical cancer with suspicious lymph nodes on imaging: a retrospective cohort study

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ABSTRACT

Objective: The optimal treatment of clinically early-stage cervical cancer with suspicious lymph nodes on pretreatment imaging is unclear. Therefore, we aimed to compare surgery (i.e., radical hysterectomy and pelvic lymphadenectomy±adjuvant therapy) with primary chemoradiotherapy as treatment strategies in this patient group regarding recurrence-free, overall survival and toxicity.
Methods: Women diagnosed between 2009–2017 with the International Federation of Gynecology and Obstetrics (2009) stage IA–IIA and suspicious nodes based on radiologic assessment of pretreatment imaging were retrospectively selected from the Netherlands Cancer Registry. Cox proportional hazard was used to estimate survival and logistic regression for toxicity. Inverse probability weighting was used to correct for confounding.

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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Grade ≥2 surgery-related (≤30 days) and grade ≥3 chemotherapy or radiotherapy-related (≤6 months) toxicity were collected. Missing data were imputed.
Results: Of 330 patients included, 131 (40%) received surgery (followed by adjuvant therapy in 54%) and 199 (60%) chemoradiotherapy. Pathological nodal status was known in 100% of the surgery group and 32% (n=63) of the chemoradiotherapy group, of whom 43% (56/131) and 89% (56/63), respectively, had metastases. After adjustment for confounders, the recurrence-free survival (hazard ratio [HR]=0.67; 95% confidence interval [CI]=0.34–1.31) and overall survival (HR=0.75; 95% CI=0.38–1.47) were not significantly different between both groups, while surgery was associated with more toxicity (odds ratio=2.82; 95% CI=1.42–5.60), mainly surgery-related.
Conclusion: In patients with clinically early-stage cervical cancer and suspicious nodes on imaging, surgery and primary chemoradiotherapy yielded comparable results in terms of survival, whereas surgery might be associated with more (surgery-related) short-term toxicity.

Keywords: Uterine Cervical Cancer; Lymph Node Metastasis; Hysterectomy; Chemoradiotherapy; Survival

Synopsis
In patients with clinically early-stage cervical cancer and suspicious nodes on imaging, radical hysterectomy with lymphadenectomy ± adjuvant therapy and primary chemoradiotherapy can achieve comparable survival outcomes, whereas surgery might be associated with more (surgery-related) short-term toxicity.

INTRODUCTION

Women with clinically early-stage cervical cancer have a 5-year survival rate of ≤92% [1,2]. This rate is negatively affected by the presence of lymph node metastasis, one of the most important prognostic factors in cervical cancer [3]. There are differences in treatment strategies for patients with International Federation of Gynecology and Obstetrics (FIGO) 2009 stage IA2–IIA2 disease and suspicious nodes on imaging. Current guidelines recommend primary chemoradiotherapy over treatment by radical hysterectomy with lymphadenectomy, followed by tailored adjuvant therapy in the presence of postoperative risk factors [4]. Research on this subject has suggested that both strategies can achieve similar survival rates [5-9]. However, these studies are mainly retrospective, with limited confounding adjustment, and rarely included only patients with suspicious nodes. Additionally, toxicity was often not evaluated in these studies, although both strategies have different toxicity profiles [10,11]. Moreover, adjuvant therapy after surgery, known as multimodality treatment, may be associated with more toxicity, such as genitourinary morbidity [8,10,11].

Today, treatment strategies are usually guided by pretreatment imaging: computed tomography (CT), magnetic resonance imaging (MRI), and/or 2-deoxy-2-[18F]fluoro-D-glucose (FDG) positron emission CT, of which the latter is generally considered superior in detecting metastatic nodes [12,13]. However, it is important to consider the risk of false-positive findings when deciding treatment strategies, as studies of pretreatment imaging (CT, MRI, and/or positron emission tomography-CT [PET-CT]) in early-stage cervical cancer have reported positive predictive values of only 47%–60% [5,14,15]. This means that

approximately half of the patients with suspicious nodes on imaging are node-negative and, therefore, could have been treated with surgery without adjuvant therapy.

Despite the increasing role of imaging in cervical cancer staging and the negative prognostic impact of nodal metastases, there remains a paucity of evidence regarding the best therapeutic approach for women with radiologic suspicious nodes. In this retrospective cohort study, we compare surgery (i.e., radical hysterectomy with lymphadenectomy±adjuvant therapy) with primary chemoradiotherapy regarding recurrence-free, overall survival and therapy-related toxicities in patients with FIGO stage IA2–IIA2 cervical cancer and radiologic suspicious nodes. Additionally, we will evaluate preoperative clinicopathologic characteristics associated with multimodality treatment.

MATERIALS AND METHODS

1. Study design and data collection

This retrospective cohort study was approved by the Privacy Review Board (#22263) of the Netherlands Cancer Registry. Data on patient-, tumor- and treatment-related characteristics were obtained from the population-based Netherlands Cancer Registry, which covers all malignancies in the Netherlands since 1989. Trained data managers collected additional data on lymph node metastases from hospital records. Eligible cervical cancer patients were 1) diagnosed between January 2009 and December 2017 because of sufficient follow-up, 2) ≥18 years at diagnosis, 3) received pretreatment imaging (CT, MRI, PET-CT, or PET-MRI), 4) had FIGO 2009 stage IA2-IIA2, 5) either squamous cell, adeno-, or adenosquamous carcinoma and 6) ≥1 suspicious lymph node(s). All patients were categorized by treatment strategy: surgery (i.e., radical hysterectomy with lymphadenectomy) or primary chemoradiotherapy. Patients treated with neoadjuvant therapy were excluded. Adjuvant (chemo)radiotherapy was administered according to local protocols and indicated in case of postoperative intermediate/high-risk factors [4,16]. Chemoradiotherapy consisted of pelvic external beam radiotherapy (i.e., 45–50 Gy) and concurrent chemotherapy (i.e., cisplatin 40 mg/m^2 weekly) or hyperthermia according to European treatment guidelines [4].

Lymph node status was registered for five anatomic regions (i.e., left/right pelvic, left/right common iliac, and para-aortic) as negative, inconclusive, suspicious or unknown, as reported by the radiologist. The short-axis diameter was recorded for inconclusive or suspicious nodes. Generally, a lymph node was considered suspicious if the short-axis diameter was ≥1.0 cm, and morphologic tumor features (e.g., central necrosis) and/or focally increased FDG-uptake were present. Imaging was performed according to local protocols, following the Dutch (Nedpas) and international (EARL) standards [17]. FIGO stage IA2 (n=3) was pooled with stage IB. Furthermore, direct conversion to FIGO 2018 was not possible due to missing information on horizontal spread.

2. Outcomes and definitions

Recurrence-free and overall survival were the primary outcomes and defined as the interval from start of primary therapy until recurrence and from diagnosis to death, respectively. Patient vital status was obtained by linkage to the Municipal Personal Records Database (updated to January 31st, 2022). Patients who were still alive were censored at that time. Recurrence status was obtained from hospital records. Patients without recurrence, or who were lost to follow-up, were censored at the last date of clinical contact. Secondary outcomes

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were therapy-related toxicity and differences in clinicopathological characteristics, stratified by presence of adjuvant treatment. Surgery-related toxicity was defined as grade ≥2 Clavien-Dindo complication ≤30 days after surgery [18]. Radiotherapy and chemotherapy related toxicities were defined as grade ≥3 Common Terminology Criteria for Adverse Events (version 4.03) complications ≤6 months after the start of treatment [19]. To identify factors that might help predict patients at risk for multimodality treatment, preoperative characteristics were compared between the surgery group with and without adjuvant therapy.

3. Statistical analysis

The Mann–Whitney U, Kruskal–Wallis, and Fisher's exact test were used for descriptive statistics. Unadjusted survival analyses were performed using the Kaplan-Meier method and the log-rank test. Missing data were considered missing at random and imputed using chained equations multiple imputation [20]. We repeated the imputation 20 times, followed by application of Rubin's rule to combine parameter estimates from multivariable Cox regression analysis [21]. We examined convergence plots and compared distributions of original and imputed data to establish validity. The proportional hazards assumption was tested by plotting scaled Schoenfeld residuals. No violations were found with an exit time of 5-years. Therefore, all survival-analyses were restricted to 5-years.

Propensity score analysis was used to control for measured heterogeneity between treatment groups, using logistic regression models to estimate the probability of treatment. These models included variables related only to the outcome of interest or to both outcome and treatment, see **Table S1**. We used different propensity score methods to determine which method achieved the best balance of covariates. An absolute standardized difference of ≤0.25 was considered to be balanced [22]. Inverse-probability-treatment-weighting was used to balance the treatment groups and control for confounding in the analyses of survival and toxicity risk using Cox and logistic regression, respectively. A subgroup analysis of toxicity was performed for patients treated with surgery, either with or without adjuvant therapy. Logistic regression analysis was used to demonstrate an association with multimodality treatment. A p-value <0.05 was considered significant, and Stata statistical software version 17.0 (StataCorp, College Station, TX, USA) was used for all analyses.

RESULTS

1. Baseline characteristics

Of 330 eligible patients, 131 (40%) received surgery (of which 85% by open approach and 15% by minimally invasive surgery) and 199 (60%) received primary chemoradiotherapy. All baseline characteristics are shown in **Table 1**. The nodal status was assessed by MRI, PET-CT, CT, and/or PET-MRI in 82%, 52%, 44% and 7%, respectively. PET-CT imaging

Table 1. Baseline characteristics of original cohort

Characteristics	Surgery (n=131)	Chemoradiotherapy (n=199)	p-value
Patient and tumor characteristics			
Median age (yr)	43 (22–77)	43 (25–81)	0.588
Charlson comorbidity index			0.480
0	102 (78)	139 (70)	
1	10 (8)	21 (11)	
≥2	3 (2)	6 (3)	
Unknown	16 (12)	33 (17)	
Smoking (yes)	45 (34)	65 (33)	0.812

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Table 1. (Continued) Baseline characteristics of original cohort

Characteristics	Surgery (n=131)	Chemoradiotherapy (n=199)	p-value
Median body mass index (kg/m^2)	24 (16–40)	24 (18–55)	0.367
Median pretreatment squamous cell carcinoma antigen (ng/mL)†	2.5 (0.2–28.9)	5.3 (0.3–93.0)	<0.001*
FIGO 2009 stage			0.041*
IA/B	162 (81)	118 (90)	
IIA	37 (19)	13 (10)	
Median clinical tumor diameter (mm)	35 (2–80)	50 (12–80)	<0.001*
Status of suspicious node			<0.001*
Suspicious	54 (41)	182 (91)	
Inconclusive	77 (59)	17 (9)	
Location of suspicious node(s)‡			<0.001*
Pelvic	115 (88)	138 (69)	
Common iliac	5 (4)	22 (11)	
Para-aortic	11 (8)	39 (20)	
Median short-axis of largest suspicious node (mm)	9 (5–50)	12 (6–43)	<0.001*
Histologic subtype			0.122
Squamous cell carcinoma	92 (70)	158 (79)	
Adeno carcinoma	33 (25)	32 (16)	
Adenosquamous cell carcinoma	6 (5)	9 (5)	
Lymphovascular space invasion			<0.001*
Absent	48 (37)	70 (35)	
Present	73 (56)	27 (14)	
Unknown	10 (8)	102 (51)	
Tumor grade			<0.001*
1	6 (5)	4 (2)	
2	59 (45)	52 (26)	
3	42 (32)	76 (38)	
Unknown	24 (18)	67 (34)	
Pathologic node status			<0.001*
Negative	75 (57)	7 (4)	
Positive	56 (43)	56 (28)	
Unknown	-	136 (68)	
Treatment characteristics			
Median removed nodes§	25 (5–57)	9 (1–44)	<0.001*
Median positive nodes¶	2 (1–33)	2 (1–20)	0.851
Nodal examination			<0.001*
Lymphadenectomy	131 (100)	36 (18)	
Debulking	-	23 (12)	
Fresh frozen section only	-	1 (1)	
Fine needle aspiration/biopsy	-	3 (2)	
No	-	136 (68)	
Surgical approach			<0.001*
Open	111 (85)	26 (42)	
Laparoscopic	20 (15)	8 (13)	
Unknown	-	28 (45)	
Nodal boosting (yes)	5 (7)	140 (70)	<0.001*
Radiotherapy volume			0.003*
Pelvic	63 (90)	152 (76)	
Pelvic + para-aortic	4 (6)	43 (22)	
Unknown	3 (4)	4 (2)	
Brachytherapy (yes)	17 (13)	195 (78)	<0.001*
Adjuvant treatment			
Chemoradiotherapy	44 (34)	-	
Radiotherapy	26 (20)	-	
Chemotherapy	1 (1)	2 (1)	
Salvage hysterectomy	-	2 (1)	
No	60 (46)	195 (98)	

Data are expressed as number of patients and (%) or median with (range).
FIGO, International Federation of Gynecology and Obstetrics.
*Statistically significant; †For squamous-cell carcinoma's only; ‡Most cranial location was decisive; §Patients with nodal examination only; ¶Patients with pathologically metastatic nodes only.

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was more common in the chemoradiotherapy group than in the surgery group (69% vs. 26%; p<0.001). Poor prognostic characteristics (i.e., higher FIGO stage, larger tumor size and nodal short-axis diameter, suspicious nodal status, higher squamous cell carcinoma antigen level, and involvement of the common iliac and para-aortic regions) were more common in the chemoradiotherapy than surgery group (p<0.001). Of all propensity score methods tested, inverse-probability-treatment-weighting achieved the best balance: all characteristics were balanced except for para-aortic region involvement, which remained more common in the chemoradiotherapy group (**Fig. S1** and **Table S1**). The distributions of the original and imputed data were consistent (**Table S2**). Pathological characteristics were more frequently missing in the chemoradiotherapy group. Including the nodal status, which was known in 100% of the surgery and 32% of the chemoradiotherapy group, of whom 43% (56/131) and 89% (56/63), respectively, had metastases. (p<0.001). This corresponded to an overall positive predictive value of 58%. As shown in **Table 1**, the chemoradiotherapy group received the most extensive treatment, with more nodal boosting (p<0.001), extended-field radiotherapy (p<0.003), and brachytherapy (p<0.001). After surgery, 54% received adjuvant therapy, with 62% receiving chemoradiotherapy.

2. Survival

Median follow-up for recurrence-free and overall survival was 49 (range, 1–134) and 90 (1–157) months after surgery and 46 (2–138) and 69 (5–156) months after chemoradiotherapy, respectively. Recurrence was observed in 26 patients (20%) after surgery and 63 patients (32%) after chemoradiotherapy (p=0.022), with pelvic metastasis (62%) and distant metastasis (42%) as most common patterns of failure (**Fig. 1**). Without adjustment for confounding, the 5-year recurrence-free and overall survival were superior for surgery (80% and 83%) compared to chemoradiotherapy (67% and 69%; p=0.003 and p=0.004). However, inverse-probability-treatment-weighting analyses showed that treatment strategy was not associated with survival, with a 5-year recurrence-free and overall survival of 81% and 82% for surgery and 75% and 76% for chemoradiotherapy (p=0.382 and p=0.392; **Fig. 2**), respectively. Multivariable analyses of original and imputed data showed similar results (**Table 2**; see **Table S3** for the complete analyses). Consistently, sensitivity analysis for patients with suspicious nodes only showed no association between treatment strategy and recurrence-free (hazard ratio [HR]=0.90; 95% confidence interval [CI]=0.47–1.74; p=0.756) or overall survival (HR=1.04; 95% CI=0.54–2.01; p=0.909).

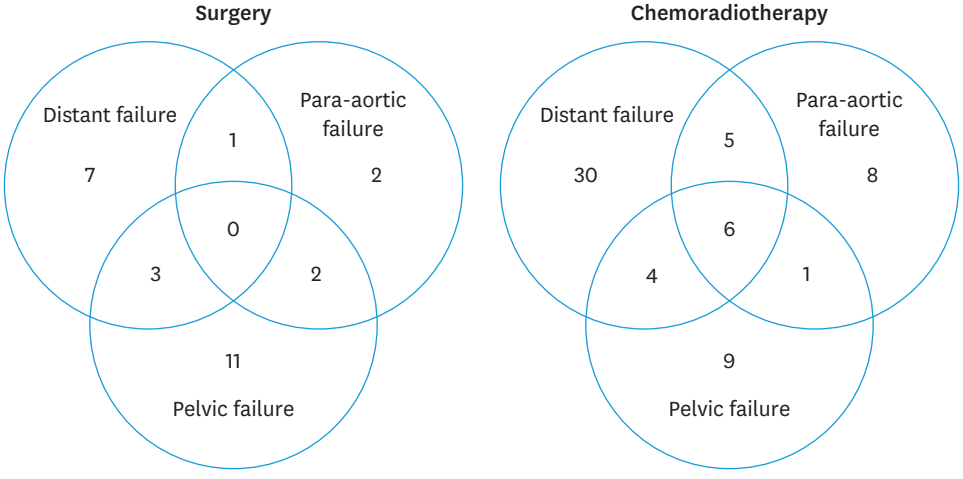

Fig. 1. Patterns of failure in patients with a recurrence after surgery (n=26) and primary chemoradiation (n=63).

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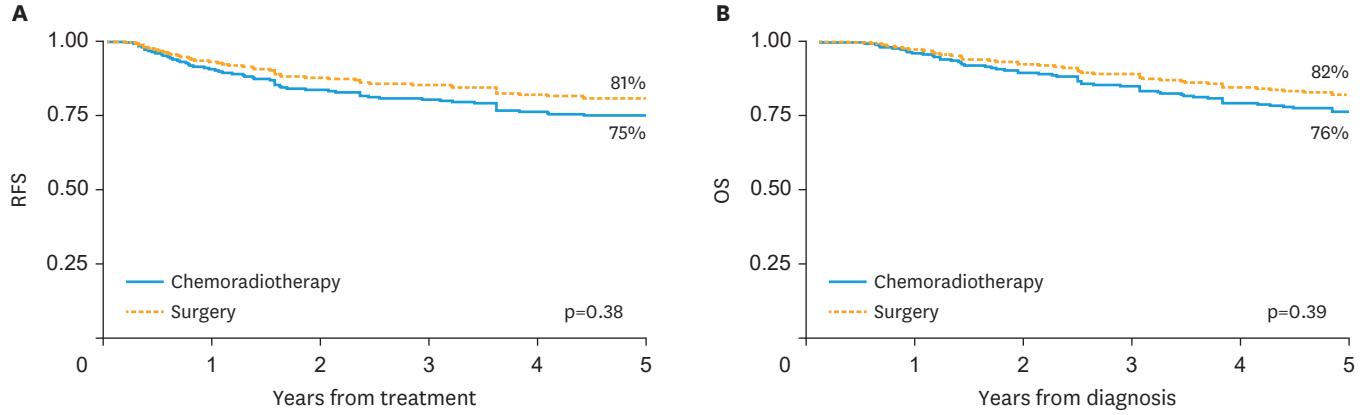

Fig. 2. Predicted survival curves from Cox proportional hazards models using inverse-probability-of treatment weighting for (A) RFS and (B) OS.
OS, overall-survival; RFS, recurrence-free survival.

Table 2. Cox regression 5-year survival analyses

Analysis type	Therapy group	Recurrence-free survival			Overall survival		
		HR	95% CI	p-value	HR	95% CI	p-value
Univariable	Chemoradiotherapy	1.00	Reference		1.00	Reference	
	Surgery	0.49	0.30–0.80	0.004*	0.54	0.35–0.84	0.006*
Multivariable original data	Chemoradiotherapy	1.00	Reference		1.00	Reference	
	Surgery	0.92	0.48–1.76	0.790	0.87	0.45–1.69	0.683
Multivariable imputed data	Chemoradiotherapy	1.00	Reference		1.00	Reference	
	Surgery	0.82	0.45–1.49	0.506	0.77	0.42–1.42	0.404
Inverse-probability-treatment-weighting Imputed data	Chemoradiotherapy	1.00	Reference		1.00	Reference	
	Surgery	0.73	0.36–1.48	0.382	0.73	0.35–1.50	0.392

CI, confidence interval; HR, hazard ratio.
*Statistically significant.

3. Toxicity

As shown in **Table 3**, more patients experienced treatment-related toxicity after surgery (34%) than after chemoradiotherapy (20%; p=0.007). This was primarily due to the post-operative complications (26%) in the surgery group, with bladder dysfunction (11%; i.e., urinary retention requiring catheterization) and infection (8%) being the most common. After chemoradiotherapy, more chemo- and radiotherapy-related toxicities were observed than after surgery (11% vs. 3%; p=0.011 and 13% vs. 6%; p=0.044, respectively). Moreover, surgery remained associated with an increased risk of toxicity after inverse-probability-treatment-weighting covariate adjustment (odds ratio [OR]=2.82; 95% CI=1.42–5.60; p=0.003). Subgroup analysis of surgery without adjuvant therapy vs. primary chemoradiotherapy showed a comparable prevalence of therapy-related toxicity (28% and 20%; p=0.213), while surgery with adjuvant therapy was associated with a higher prevalence (38%; p=0.011).

4. Multimodality treatment

The surgery group (n=131) was subdivided into two groups: with (n=71) and without (n=60) adjuvant treatment. Among preoperative characteristics, lymphovascular space invasion and depth of invasion differed significantly between both groups (**Table S4**). Adjuvant treatment was associated with: lymphovascular space invasion (OR=6.0; 95% CI=2.7–13.4), depth of invasion ≥15 mm (OR=2.5; 95% CI=1.1–5.8), tumors >4 cm on MRI (OR=6.0; 95% CI=1.4–26.4), and a suspicious nodal status (OR=2.1; 95% CI=1.0–4.3).

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Table 3. Therapy-related toxicities

Toxicities	Surgery (n=131)	Chemoradiotherapy (n=199)	p-value
Surgery-related			
Intra-operative injury	3 (2)	2 (1)	0.389
Infection	11 (8)	-	<0.001*
Thromboembolism	2 (2)	-	0.157
Intensive-care admission	1 (1)	1 (1)	1.00
Bladder dysfunction	15 (11)	-	<0.001*
Blood transfusion	7 (5)	1 (1)	0.007*
Other	5 (4)	-	0.009*
Total patients	34 (26)	2 (1)	<0.001*
Radiotherapy-related			
Urological	1 (1)	3 (2)	1.00
Gastro-intestinal	2 (2)	12 (6)	0.053
Genital	-	2 (1)	0.520
Other	2 (2)	5 (3)	0.707
Total patients	4 (3)	21 (11)	0.011*
Chemotherapy-related			
Nausea/vomiting	1 (1)	10 (5)	0.055
Nephrotoxicity	2 (2)	1 (1)	0.565
Mucositis/stomatitis	2 (2)	-	0.157
Bone marrow depression	-	4 (2)	0.155
Malaise/fatigue	-	2 (1)	0.520
Neurotoxicity	-	2 (1)	0.520
Other	5 (4)	11 (6)	0.604
Total patients	8 (6)	26 (13)	0.044*
Total patients with therapy-related toxicity	44 (34)	40 (20)	0.007*

Values are presented as number (%).
*Statistically significant.

DISCUSSION

This study compared surgery with primary chemoradiotherapy as a treatment strategy for women with FIGO stage IA–IIA2 cervical cancer and suspicious lymph nodes on pretreatment imaging. The chemoradiotherapy group included more patients with poor prognostic characteristics than the surgery group and therefore had worse survival outcomes. However, after adjustment for confounders, recurrence-free and overall survival were not significantly different between the two strategies. Additionally, surgery was associated with more short-term toxicity due to postoperative complications and multimodality treatment. Of note, only half (54%) of patients received adjuvant therapy after surgery, supporting the low predictive value of suspicious nodes on pretreatment imaging (58%). Preoperative characteristics (i.e., lymphovascular space invasion, depth of invasion, tumor size on MRI, and radiologic nodal status) may help guide treatment decisions by predicting patients at risk for multimodality treatment.

Surgery and primary chemoradiotherapy seem equally effective regarding survival outcomes, supporting evidence from previous observations [5,7-9,23]. The only randomized controlled trial comparing both strategies included only a few patients with suspicious nodes on imaging (13%), and radiotherapy was not combined with chemotherapy, as this study dates from 1997 [9]. Therefore, this study does not provide evidence of treatment strategies for our study cohort. More recently, Park et al. [5] retrospectively compared radical hysterectomy (n=195) with chemoradiotherapy (n=67) in a cohort with suspicious nodes, using propensity score matching (n=33) for age, histology, and vaginal invasion, and found no differences in 5-year disease-free (81%–83%) and overall survival (≤89%) between the two treatments.

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These survival rates are comparable to ours, including the overall recurrence rate (24%–26% vs. 27%). However, we found more distant relapses after chemoradiotherapy, possibly explained by the poorer prognostic characteristics of our group. Survival comparability of both treatment strategies in early-stage cervical cancer has been suggested previously, although cohorts varied with respect to prognostic factors (e.g., tumor size, suspicion of parametrial invasion or nodal metastases) across studies [7,8]. Unlike previous analyses, we adjusted for more relevant confounders and included a larger cohort of patients with suspicious nodes only. Additionally, we assessed therapy-related toxicity since both strategies were expected to have different toxicity profiles.

The prevalence of toxicity in our two treatment groups lies within the range reported by others: 10%–30% grade ≥3 toxicities after surgery and 15%–59% after chemoradiotherapy [7,11,24,25]. These broad ranges possibly result from varying toxicity-scoring systems across studies. Our results suggest that surgery is associated with more short-term toxicity. However, most of these toxicities consist of postoperative complications, including blood transfusion, infection, and bladder dysfunction, which are often (partially) reversible [26,27]. Chemoradiotherapy was associated with more radiotherapy-related toxicity, which is often characterized by its late and long-term occurrence (e.g., gastrointestinal, genitourinary, and fistula) [28]. Moreover, the risk of short-term toxicity after surgery without adjuvant therapy was comparable to primary chemoradiotherapy. The detrimental effect of multimodality treatment on toxicity has been described previously and may be related to inaccurate staging [24,25,29]. Potential strategies to reduce the risk of multimodality treatment include pretreatment pathologic evaluation of suspicious nodes (e.g., image-guided fine-needle cytology/biopsy or debulking) or treatment guidance based on clinicopathologic characteristics. Patients with lymphovascular space invasion, depth of invasion ≥15 mm, tumors >4 cm on MRI, and suspicious nodes on pretreatment imaging are likely to require multimodality treatment and could therefore be referred for primary chemoradiotherapy. Previous studies have shown that lymphovascular space invasion, depth of invasion, and tumor size are associated with nodal involvement, poor prognosis, and the need for adjuvant treatment [16,30].

Another point worth discussing is the approach of the radical hysterectomy, which can be performed by open or minimally invasive surgery. During the tie period of our study, minimally invasive surgery gained popularity and 15% of our surgical cohort had surgery using this approach. In 2018, the prospective, randomized LACC trial showed that minimally invasive radical hysterectomy is associated with worse survival for tumors >2 cm [31]. As a result, an open approach has become the standard of care, whereas a minimally invasive approach may be considered in low-risk tumors, preferably in a research setting [4,32]. Since 2018, several retrospective studies have reported conflicting results, including similar survival rates for both approaches [33,34]. In addition, two trials comparing robotic-assisted radical hysterectomy with open radical hysterectomy are currently open for enrolment to provide further evidence on the safety of minimally invasive surgery [35,36]. A major limitation of this study is confounding by disease severity, reflected by heterogeneity in baseline characteristics between treatment groups. This bias was expected, as larger tumors and lymph node metastases are indications for primary chemoradiotherapy [4]. Adjustment by inverse-probability-treatment-weighting resulted in a more balanced analysis of covariates. However, unmeasured variables (e.g., deep invasion and multiple suspicious nodes) may still be unbalanced. Additionally, our analyses contained up to 38% missing data, which could be considered a limitation. However, we used multiple imputation, which has been described

as a reliable approach to handling missing data, even for large proportions [20]. In fact, the estimates after imputation were more accurate than those of complete case analysis. Another limitation concerns our toxicity outcome, which was dependent on hospital record reporting and limited to the first six months after treatment due to time-consuming retrospective recording. Consequently, our radiotherapy-related toxicity may be underestimated by missing late-term events (e.g., fistula, stricture, and chronic enteritis), which may have biased our toxicity results. Finally, whether and how therapy-related toxicity affects the quality of life in both treatment groups remains unanswered and should be addressed in future research.

Despite its limitations, this study provides more insight into the outcome of treatment strategies for patients with FIGO 2009 stage IA-IIA cervical cancer and suspicious nodes on imaging. First, poor prognostic factors (e.g., higher FIGO stage and squamous cell carcinoma antigen level, larger tumor and node size, and para-aortic node involvement) may guide treatment choice toward chemoradiotherapy. Second, if radical surgery is feasible, it seems to be an equally effective treatment strategy in terms of survival. Third, surgery and chemoradiotherapy have different toxicity profiles, highlighting the need for counselling with shared decision-making. In addition, avoiding multimodality treatment by better predicting the need for adjuvant therapy based on clinicopathologic characteristics, may reduce the risk of toxicity. These results must be interpreted with caution, because they are based on retrospective data and are subject to bias due to unmeasured confounding. However, prospective randomization may not be feasible because large sample sizes will be required, as retrospective studies have failed to demonstrate superiority of either strategy. Additionally, possible patient and physician preferences for one of the two treatment strategies may further complicate enrollment. Future studies could focus on improving pretreatment detection of metastatic nodes and thereby tailoring treatment decisions, (e.g., pathologic evaluation of suspicious nodes, advanced imaging techniques, radiomics, or nomograms).

In conclusion, in patients with clinically early-stage cervical cancer and suspicious nodes on imaging, both surgery and primary chemoradiotherapy yielded comparable results in terms of recurrence-free and overall survival. As both strategies are associated with different short-term toxicity profiles, shared decision-making seems to be the best approach for patients with suspicious nodes. Furthermore, preoperative clinicopathologic characteristics may help to select patients at risk for multimodality treatment.

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SUPPLEMENTARY MATERIALS

Table S1

Baseline characteristics before and after inverse-probability-treatment-weighting analysis regarding survival and toxicity

Table S2

Data distribution before and after multiple imputation

Table S3

Multivariable Cox-regression and inverse-probability-treatment-weighting analysis regarding RFS and OS of original and imputed data

Table S4

Preoperative clinicopathological characteristics of patients with or without adjuvant treatment after surgery

Fig. S1

Standardized difference of propensity score model covariates before and after adjustment for: (A) survival and (B) toxicity.

REFERENCES

1. American Cancer Society. Cancer facts & figures [Internet]. Atlanta, GA: American Cancer Society; 2020 [cited 2022 Nov 21]. Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf.
2. Integraal Kankercentrum Nederland. Baarmoederhalskanker in Nederland - trends en cijfers uit de Nederlandse Kankerregistratie [Internet]. Utrecht: Integraal Kankercentrum Nederland; 2023 [cited 2023 Jun 6]. Available from: https://iknl.nl/cervixcarcinoom-in-nederland.
3. Sakuragi N. Up-to-date management of lymph node metastasis and the role of tailored lymphadenectomy in cervical cancer. Int J Clin Oncol 2007;12:165-75. PUBMED | CROSSREF
4. Cibula D, Pötter R, Planchamp F, Avall-Lundqvist E, Fischerova D, Haie Meder C, et al. The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer. Radiother Oncol 2018;127:404-16. PUBMED | CROSSREF
5. Park J, Kim YJ, Song MK, Nam JH, Park SY, Kim YS, et al. Definitive chemoradiotherapy versus radical hysterectomy followed by tailored adjuvant therapy in women with early-stage cervical cancer presenting with pelvic lymph node metastasis on pretreatment evaluation: a propensity score matching analysis. Cancers (Basel) 2021;13:3703. PUBMED | CROSSREF
6. Tomita N, Mizuno M, Makita C, Kondo S, Mori M, Sakata J, et al. Propensity score analysis of radical hysterectomy versus definitive chemoradiation for FIGO stage IIB cervical cancer. Int J Gynecol Cancer 2018;28:1576-83. PUBMED | CROSSREF
7. Zivanovic O, Alektiar KM, Sonoda Y, Zhou Q, Iasonos A, Tew WP, et al. Treatment patterns of FIGO Stage IB2 cervical cancer: a single-institution experience of radical hysterectomy with individualized postoperative therapy and definitive radiation therapy. Gynecol Oncol 2008;111:265-70. PUBMED | CROSSREF
8. Kong TW, Lee JD, Son JH, Paek J, Chun M, Chang SJ, et al. Treatment outcomes in patients with FIGO stage IB–IIA cervical cancer and a focally disrupted cervical stromal ring on magnetic resonance imaging: a propensity score matching study. Gynecol Oncol 2016;143:77-82. PUBMED | CROSSREF
9. Landoni F, Maneo A, Colombo A, Placa F, Milani R, Perego P, et al. Randomised study of radical surgery versus radiotherapy for stage Ib–IIa cervical cancer. Lancet 1997;350:535-40. PUBMED | CROSSREF
10. Wenzel HHB, Olthof EP, Bekkers RLM, Boere IA, Lemmens VE, Nijman HW, et al. Primary or adjuvant chemoradiotherapy for cervical cancer with intraoperative lymph node metastasis - a review. Cancer Treat Rev 2022;102:102311. PUBMED | CROSSREF
11. Derks M, Groenman FA, van Lonkhuijzen LR, Schut PC, Westerveld H, van der Velden J, et al. Completing or abandoning radical hysterectomy in early-stage lymph node-positive cervical cancer: impact on disease-free survival and treatment-related toxicity. Int J Gynecol Cancer 2017;27:1015-20. PUBMED | CROSSREF
12. Selman TJ, Mann C, Zamora J, Appleyard TL, Khan K. Diagnostic accuracy of tests for lymph node status in primary cervical cancer: a systematic review and meta-analysis. CMAJ 2008;178:855-62. PUBMED | CROSSREF
13. Liu B, Gao S, Li S. A comprehensive comparison of CT, MRI, positron emission tomography or positron emission tomography/CT, and diffusion weighted imaging-MRI for detecting the lymph nodes metastases in patients with cervical cancer: a meta-analysis based on 67 studies. Gynecol Obstet Invest 2017;82:209-22. PUBMED | CROSSREF

14. Staley SA, Tucker KR, Gehrig PA, Clark LH. Accuracy of preoperative cross-sectional imaging in cervical cancer patients undergoing primary radical surgery. Gynecol Oncol 2021;160:384-8. PUBMED | CROSSREF
15. Vermolen PC, van Trommel NE, Vogel WV, Adam JA, van der Velden J, Mom CH. The issue of false positive lymph nodes on [18F] FDG-PET/CT for cervical carcinoma and consequences for treatment. Eur J Gynaecol Oncol 2021;42:943-50. CROSSREF
16. Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a Gynecologic Oncology Group Study. Gynecol Oncol 1999;73:177-83. PUBMED | CROSSREF
17. Boellaard R, Oyen WJ, Hoekstra CJ, Hoekstra OS, Visser EP, Willemsen AT, et al. The Netherlands protocol for standardisation and quantification of FDG whole body PET studies in multi-centre trials. Eur J Nucl Med Mol Imaging 2008;35:2320-33. PUBMED | CROSSREF
18. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13. PUBMED | CROSSREF
19. National Cancer Institute. Common terminology criteria for adverse events: (CTCAE). Bethesda, MD: National Cancer Institute; 2010.
20. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. Stat Med 2011;30:377-99. PUBMED | CROSSREF
21. Leyrat C, Seaman SR, White IR, Douglas I, Smeeth L, Kim J, et al. Propensity score analysis with partially observed covariates: how should multiple imputation be used? Stat Methods Med Res 2019;28:3-19. PUBMED | CROSSREF
22. Garrido MM, Kelley AS, Paris J, Roza K, Meier DE, Morrison RS, et al. Methods for constructing and assessing propensity scores. Health Serv Res 2014;49:1701-20. PUBMED | CROSSREF
23. Kong TW, Lee JD, Son JH, Paek J, Chun M, Chang SJ, et al. Corrigendum to 'Treatment outcomes in patients with FIGO stage IB–IIA cervical cancer and a focally disrupted cervical stromal ring on magnetic resonance imaging: a propensity score matching study' [Gynecol. Oncol. 143 (2016) 77-82] Gynecol Oncol 2017;144:228. PUBMED | CROSSREF
24. Machida H, Matsuo K, Furusawa A, Kita T, Kitagawa R, Mikami M. Profile of treatment-related complications in women with clinical stage IB–IIB cervical cancer: a nationwide cohort study in Japan. PLoS One 2019;14:e0210125. PUBMED | CROSSREF
25. Park JY, Kim DY, Kim JH, Kim YM, Kim YT, Kim YS, et al. Comparison of outcomes between radical hysterectomy followed by tailored adjuvant therapy versus primary chemoradiation therapy in IB2 and IIA2 cervical cancer. J Gynecol Oncol 2012;23:226-34. PUBMED | CROSSREF
26. Naik R, Nwabinelli J, Mayne C, Nordin A, de Barros Lopes A, Monaghan JM, et al. Prevalence and management of (non-fistulous) urinary incontinence in women following radical hysterectomy for early stage cervical cancer. Eur J Gynaecol Oncol 2001;22:26-30. PUBMED
27. Ceccaroni M, Roviglione G, Spagnolo E, Casadio P, Clarizia R, Peiretti M, et al. Pelvic dysfunctions and quality of life after nerve-sparing radical hysterectomy: a multicenter comparative study. Anticancer Res 2012;32:581-8. PUBMED
28. Pötter R, Tanderup K, Schmid MP, Jürgenliemk-Schulz I, Haie-Meder C, Fokdal LU, et al. MRI-guided adaptive brachytherapy in locally advanced cervical cancer (EMBRACE-I): a multicentre prospective cohort study. Lancet Oncol 2021;22:538-47. PUBMED | CROSSREF
29. Landoni F, Colombo A, Milani R, Placa F, Zanagnolo V, Mangioni C. Randomized study between radical surgery and radiotherapy for the treatment of stage IB-IIA cervical cancer: 20-year update. J Gynecol Oncol 2017;28:e34. PUBMED | CROSSREF
30. Olthof EP, van der Aa MA, Adam JA, Stalpers LJA, Wenzel HHB, van der Velden J, et al. The role of lymph nodes in cervical cancer: incidence and identification of lymph node metastases-a literature review. Int J Clin Oncol 2021;26:1600-10. PUBMED | CROSSREF
31. Ramirez PT, Frumovitz M, Pareja R, Lopez A, Vieira M, Ribeiro R, et al. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. N Engl J Med 2018;379:1895-904. PUBMED | CROSSREF
32. Cibula D, Raspollini MR, Planchamp F, Centeno C, Chargari C, Felix A, et al. ESGO/ESTRO/ESP guidelines for the management of patients with cervical cancer - update 2023. Int J Gynecol Cancer 2023;33:649-66. PUBMED | CROSSREF
33. Bogani G, Di Donato V, Scambia G, Raspagliesi F, Chiantera V, Sozzi G, et al. Radical hysterectomy for early stage cervical cancer. Int J Environ Res Public Health 2022;19:11641. PUBMED | CROSSREF
34. Wenzel HHB, Smolders RGV, Beltman JJ, Lambrechts S, Trum HW, Yigit R, et al. Survival of patients with early-stage cervical cancer after abdominal or laparoscopic radical hysterectomy: a nationwide cohort study and literature review. Eur J Cancer 2020;133:14-21. PUBMED | CROSSREF

35. Bixel KL, Leitao MM, Chase DM, Quick A, Lim PC, Eskander RN, et al. ROCC/GOG-3043: a randomized non-inferiority trial of robotic versus open radical hysterectomy for early-stage cervical cancer. J Clin Oncol 2022;40:TPS5605. CROSSREF
36. Falconer H, Palsdottir K, Stalberg K, Dahm-Kähler P, Ottander U, Lundin ES, et al. Robot-assisted approach to cervical cancer (RACC): an international multi-center, open-label randomized controlled trial. Int J Gynecol Cancer 2019;29:1072-6. PUBMED | CROSSREF